PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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SUISSE

12 SEP. 2005

PCT

WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rule 66)

Date of mailing *(day/month/year)*	08.09.2005
Applicant's or agent's file reference: 14673/PCT	**REPLY DUE** **within 1 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/002165	30.06.2004	30.06.2003

International Patent Classification (IPC) or both national classification and IPC
C07K14/47, C12N15/12, A61K47/42, A61K38/17, A61P35/00

Applicant
UNIVERSITE DE LAUSANNE et al.

1. ☒ The written opinion established by the International Searching Authority:
   ☒ is ☐ is not
   considered to be a written opinion of the International Preliminary Examining Authority

2. This second report contains indications relating to the following items:
   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

   When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(e).
   How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.
   Also: For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*. For an informal communication with the examiner, see Rule 66.6. For an additional opportunity to submit amendments, see Rule 66.4.
   If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary report on patentability (Chapter II of the PCT) must be established according to Rule 69.2 is: 30.10.2005

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Madruga, J Telephone No. +31 70 340-3121

WRITTEN OPINION OF THE INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

International application No.
PCT/IB2004/002165

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this opinion is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

   Description, Pages

   1-31 as originally filed

   Sequence listings part of the description, Pages

   1-6 received on 01.10.2004 with letter of 28.09.2004

   Claims, Numbers

   1-29 filed with the demand

   Drawings, Sheets

   1/8-8/8 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on01.10.2004

2. ☒In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 24-27 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. claims 24-27 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search opinion has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See supplemental sheet for further details

Box No. V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1, 2, 11-13, 20, 21, 26-29
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-29
Industrial applicability (IA)	Yes:	Claims	1-23, 28-29
	No:	Claims	

2. Citations and explanations:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

1. Claims **24-27** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

2. The following documents are referred to in this communication:

D1 : WO 94/03597 A (DUCHESNE MARC ; TOCQUE BRUNO (FR); RHONE POULENC RORER SA (FR); SCHWEI) 17 February 1994 (1994-02-17)

D2 : WO 03/018630 A (FRENCH JULIET ; KENNEDY DEREK (AU); UNIV GRIFFITH (AU); HART DEREK (AU) 6 March 2003 (2003-03-06)

D3 : DUCHESNE M ET AL: "Identification of the SH3 domain of GAP as an essential sequence for Ras_GAP-mediated signaling" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 259, 22 January 1993 (1993-01-22), pages 525-528, XP002092187 ISSN: 0036-8075

D4 : YANG JIANG-YAN ET AL: "Antiapoptotic signaling generated by caspase-induced cleavage of RasGAP" MOLECULAR AND CELLULAR BIOLOGY, vol. 21, no. 16, August 2001 (2001-08), pages 5346-5358, XP002296743 ISSN: 0270-7306

D5: LEBLANC VERONIQUE ET AL: "Ras-GTPase activating protein inhibition specifically induces apoptosis of tumour cells" ONCOGENE, vol. 18, no. 34, August 1999 (1999-08), pages 4884-4889, XP002296744 ISSN: 0950-9232

D6: SCHWARZE S ET AL: "In vivo protein transduction: delivery of a biologically active protein into the mouse" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 285, no. 5433, 3 September 1999 (1999-09-03), pages 1569-1572, XP002140133 ISSN: 0036-8075

3. **NOVELTY (Art. 33(2) PCT)**

3.1 D4 discloses that a peptide consisting of amino acids 158 to 455 of RasGAP (N2 fragment, produced by RasGAP caspase cleavage), potentiates apoptosis and cell killing in genotoxin-treated tumor cells (HeLa cells; see page 5351, left-hand column, paragraph 2 to page 5354, right-hand column, paragraph 5, figures). The activity to enhance the ability of a drug to kill cells is an inherent property of the peptides. The compositions used in D4 are regarded as pharmaceutical compositions.

3.2 Optional or preferred features have no limiting effect on the scope of the claims (e.g. claims 16, 29; PCT Guidelines Part II-5.40).

3.3 Thus, the present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims **1, 2, 11-13, 20, 21, 26-29** is not new in respect of the prior art as defined in the regulations (Rule 64(1)-(3) PCT).

4. INVENTIVE STEP (Art. 33(3) PCT)

4.1 **Dependent claims 3-5**, refer to a pharmaceutical composition as in claim 1, wherein the N2 sequence comprises the SH3 domain and has at least 70 amino acids, preferably selected from SEQ ID Nos: 1-4, preferably having the sequence WXWVTXXRTX.

4.1.1 D4 is regarded as the closest prior art. The difference with the application is that in the application, the active sequence in the N2 sequence of the RasGap protein, responsible for the enhancement of genotoxins to kill cancer cells is identified. The problem to be solved by the subject-matter of dependent claims 3-5 is to delimit the region in N2 responsible for the enhancement of the genotoxin ability to kill cells. The solution is the inclusion in the pharmaceutical compositions of a peptide comprising the WMWVTNLRTD sequence.

NO - selectivity?

4.1.2 D1 discloses a peptide consisting of the sequence WMWVTNLRTD (P5, SEQ ID NO: 5), and peptides comprising the sequence WMWVTNLRTD (peptides P6 and P8) which are capable of inhibiting the transformation activity of the Ras protein (D1, example 3). D1 claims the use of said peptides in pharmaceutical

compositions for the treatment of cancer. D1 discloses nucleic acid molecules encoding said peptides, vectors comprising said nucleic acids and host cells containing said peptide and said nuclei acid.

4.1.3 A skilled person with knowledge of D4, would also be aware of D1 since it belongs to the same technical field and would derive from D1 the peptide which inhibits Ras-Gap. The skilled person would combine the teachings of D4 and D1 and arrive to the solution proposed in claims **3-5**, whose subject-matter is therefore not regarded as inventive in the sense of Article 33(2) and (3) PCT.

4.1.4 D2 discloses a peptide of 61 amino acids (D2, SEQ ID NO: 6, page 51, claim 22), which comprises the polypeptide encoded by SEQ ID NO: 4 of the present application (WMWVTNLRTD); said peptide is a mimetic which disrupts or prevents formation of a complex between the NTF2-like domain of G3BP-2 and an endogenous target peptide, for example rasGAP120; D2 claims the use thereof for breast cancer therapy (claim 34). The teachings of D2 could also be used by the skilled person in combination with D4 to arrive to the solution proposed in claims 3-5.

4.2 **Dependent claims 6-10**, referring to a peptide according to present claim 1 conjugated to an agent which increases accumulation in the cell, said agent being preferably HIV-TAT $_{48-57}$ peptide, do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (Article 33(2) and (3) PCT).

4.2.1 D4 is regarded as the closest prior art. The **problem** of improving the delivery of peptides derived from the N2 fragment of RasGAP to the cells, is **solved** in the application by conjugating said peptides to the HIV-TAT $_{48-57}$ peptide. A skilled person with knowledge of D6 would know that such a HIV-TAT $_{48-57}$ peptide is suitable for this purpose and would combine the teachings of D4 and D6 to arrive to the subject-matter of claims **6-10**.

4.2.2 It appears that other carriers might be used; the choice of one of them is considered as just one of several possibilities for a skilled person in view of a lack of any especial advantages or surprising properties which might justify an

inventive step.

4.3 The subject-matter of dependent claims **14-19**, concerning specific genotoxins is not regarded as inventive since it represents a selection of many alternative possible genotoxins which would be known for the skilled person and which do not seems to have any specific technical effect in the context of the present application.

4.4 The use of the composition for a long list of cancers types in claims **22-25** is not regarded as a technical feature sufficient to render the subject-matter of said claims inventive over D4.

4.5 The present application does therefore not satisfy the criterion set forth in Article 33(3) PCT and the subject-matter of claims **1-29** does not involve an inventive step (Rule 65(1)(2) PCT).

4.6 Not all drugs induce apoptosis in cells and therefore, it appears highly unlikely that the peptides according to the invention would enhance the ability of "any drug" to kill selectively cancer cells. The application provides support only for genotoxins. It seems at present that only a pharmaceutical composition comprising a combination of specific **peptides smaller that N2 and comprising the subsequence WMWVTNLRTD** and a **genotoxin** for enhancing apoptosis /killing **specifically in cancer cells** would not seem obvious over the available prior art.

5. INDUSTRIAL APPLICABILITY (Art. 33(4) PCT)

5.1 For the assessment of the present claims **24-27** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment (Rule 39.1(iv) PCT).

VIII Certain observations on the international application

6. The application does not meet the requirements of Article 6 PCT because the independent claims are not clear for the following reasons:

6.1 Although the application discloses a peptide with homology to the WMWVTNLRTD sequence in the insect RasGAP protein (WLWVTAHRTG), no evidence is given that such a peptide also has the activity of enhancing the ability of a dug to kill cancer cells. No such evidence is given either for any of all the possible peptides (WxWVTxxRTx) other than for WMWVTNLRTD. Thus, subject-matter other than that concerning the peptides encoded by SEQ ID NOs: 1-4 (including WMWVTNLRTD) and to the peptide WLWVTAHRTG lacks support in the sense of Art. 6 PCT and does not seem to be sufficiently disclosed in the sense of Art. 5 PCT.

6.2 It appears from the description as a whole and in particular from table 2, that the presence of the sequence WMWVTNLRTD in the peptides claimed is an essential technical feature of the present invention. This essential technical feature is however not present in any of the independent claims. For these reasons the claims lack clarity according to Art. 6 PCT taken in combination with Rule 6.3 (b) PCT (see also PCT Preliminary Examination Guidelines Part II 5.4-5).

6.3 In addition, due to the broad definition of the terms "fragments", variants" and "part", the only technical feature remaining in the independent claims is the functional definition, namely that the peptide should enhance the ability of a drug to selectively kill cancer cells. This is considered to be a definition in terms of a result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result are however missing. Thus, none the independent claims meets the requirements of Article 6 PCT.